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Review Article

Single-pill combination for treatment of hypertension: Just a matter of practicality or is there a real clinical benefit?

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ABSTRACT

Elevated blood pressure (BP) is the largest contributor to the incident cardiovascular disease worldwide. Despite explicit guideline recommendations for the diagnosis and management of hypertension, a large proportion of patients remain undiagnosed, untreated, or treated but uncontrolled. Inadequate BP control is associated with many complex factors including patient preference, physician's inertia, health systems disparities, and poor adherence to prescribed antihypertensive drug treatment. The primary driver for reduced cardiovascular morbidity and mortality is lowering of BP "per se'' and not class effects of specific pharmacotherapies. The recent ESH guidelines recommend the use of four major classes of drugs including renin-angiotensin-aldosterone system (RAS) blockers (angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEi)), calcium channel blockers (CCB), thiazide and thiazide-like diuretics, and betablockers. Initiation of treatment for hypertension with a two-drug regimen, preferably in a single pill combination (SPC), is recommended for most patients. Preferred combinations should comprise a RAS blocker (either an ACEi or an ARB) with a CCB or thiazide/thiazide-like diuretic. These strategies are supported by robust evidence that combination therapy produces greater BP reductions than monotherapy, reduces side effects of the individual components, improves therapeutic adherence and long-term persistence on treatment, and permits achievement of earlier BP control.

1. Introduction

Cardiovascular disease (CVD) represents the leading cause of morbidity and mortality worldwide resulting in approximately one third of all deaths globally [1,2]. Despite significant advances in health care over the last 60 years, the global CVD burden continues to increase due to higher prevalence of CVD risk factors. In the US diabetes and obesity increased among young adults from 2009 to March 2020, while hypertension did not change and hyperlipidaemia declined [3,4]. However, in medium and low-income countries all CV risk factors tend to increase [5–7]. This statistic is projected to worsen in next few years and therefore needs to be urgently addressed. Importantly, a large proportion of these CVD related deaths are driven by five modifiable CVD risk factors (hypertension, dyslipidaemia, type 2 diabetes, obesity and smoking), with elevated systolic blood pressure being the largest contributor to population-attributable factors of incident CVD events in all regions [8].

Despite guideline recommendations for screening, diagnosis and management of hypertension, a large proportion of patients remain undiagnosed or undertreated. Low adherence and persistence to both lifestyle changes and antihypertensive drug treatment are some of the most important causes of poor BP control worldwide [9,10]. Although hypertension guidelines provide clear recommendations to overcome these problems, implementation is hampered by barriers at different levels: the patient preferences, suboptimal adherence to antihypertensive drug treatment, physician's inertia, and the disparities of health systems. Underestimation of the impact of uncontrolled hypertension and limited health literacy lead to low adherence and persistence among patients, treatment inertia by physicians and lack of decisive healthcare system action. Even though causes of poor BP control rates are multifactorial, one simple way to achieve better BP control is to use fixed-dose combination therapy, in which two or more classes of BP medications are present in a single pill or capsule (SPC). This approach has been

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woefully underutilized, increasing use of SPC therapy could drastically improve hypertension control and reduce cardiovascular morbidity and mortality in both high- and low-income countries.

The ESH guidelines recommend the use of four major classes of antihypertensive agents in clinical practice: a) renin-angiotensin-aldosterone system (RAAS) blockers, including angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEi); b) calcium channel blockers (CCB); c) thiazide and thiazide-like diuretics (DIU); and d) beta-blockers. As summarized in Table 1, many international guidelines recommend initiation of antihypertensive treatment with a SPC containing a RAAS blocker (ARB or ACEi) and a dihydropyrine CCB or a thiazide/thiazide-like diuretic for most patients. Monotherapy should be reserved for patients with low atherosclerotic CVD risk (ASCVD) and BP < 150/95 mmHg, or high-normal BP and very high CV risk, or frail patients and/or advanced age [12–15]. The inclusion of beta-blockers (particularly those exhibiting beta1-selectivity and an additional direct vasodilating property) as part of the major antihypertensive drug classes to start treatment in the 2023 ESH guidelines has received some criticisms because these drugs are less effective in preventing stroke and cardiovascular mortality [16]. However, the Task Force of the ESH guidelines consider that beta-blockers should be at initiation of treatment in patients with specific clinical conditions such as heart failure with reduced ejection fraction (HFrEF), chronic coronary syndromes, post-myocardial infarction, and atrial fibrillation requiring heart rate control. Moreover, in low risk hypertensive patients with elevated resting heart rate > 80 bpm, and younger hypertensive women planning pregnancy or already pregnant may be used in monotherapy or combination. These reasons justify the position of beta-blockers as one of the major antihypertensive drug classes [15].

These recommendations are supported by robust evidence that combination therapy produces greater BP reductions than monotherapy, reduces side effects of the individual components, improves therapeutic adherence and long-term persistence on treatment, and achieves earlier BP control. This article provides an overview of the clinical evidence supporting this strategy to achieve better BP control and reduce cardiovascular events.

Table 1
Recommendations of the most recent guidelines about the use of combination therapy of antihypertensive drugs in a single pill to start treatment in most patients.

Guideline	Combination treatment recommendation	Recommendation of single pill combination
2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults [11].	Initiation of antihypertensive drug therapy with 2 first-line agents of different classes (thiazide diuretics, calcium channel blockers (CCB), and angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), either as separate agents or in fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their target.	Use of single pill combinations (SPC) rather than free individual components (FCT) can be useful to improve adherence to antihypertensive therapy. In adults with hypertension, dosing of antihypertensive medication once daily rather than multiple times daily is beneficial to improve adherence.
2018 ESC/ESH Guidelines for the management of arterial hypertension [12]. 2023 ESH Guidelines for the management of arterial hypertension [15].	Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACEi or an ARB), with a CCB or a thiazide diuretic. Other combinations of the five major classes can be used. In black patients, initial antihypertensive treatment should include a diuretic or a CCB, either in combination with a thiazide diuretic or a RAS blocker.	It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a SPC. The exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg). It is recommended that a two-drug combination, usually as an SPC, is used as initial therapy for most black patients.

RAS: Renin angiotensin system; SBP: Systolic blood pressure.

2. Combination treatment produces greater blood pressure reduction than monotherapy

The pathophysiologic processes leading to elevated blood pressure and hypertension are multifactorial, including abnormal activation of neurohormonal pathways such as the renin angiotensin aldosterone system, symptomatic nervous system, and increased intravascular sodium levels and blood volume. Accordingly, one of the primary reasons for the superior efficacy of combination therapy is that it targets multiple physiological pathways. A landmark meta-analysis by Wald, et al. of nearly 11,000 participants from 42 clinical trials examined the efficacy of mono- versus combination antihypertensive therapy [17]. They demonstrated that monotherapies, including traditional first line agents such as thiazide diuretics, ACE inhibitors, and calcium channel blockers, lowered systolic blood pressure (SBP) by approximately 7–8 mm Hg. However, when combined with any other anti-hypertensive medication, SBP was reduced by an additional 7 mm Hg. Furthermore, when they compared the efficacy of doubling the dose of a single medication versus adding a new class of BP lowering medication, the latter was associated with five times greater reduction in SBP ($p < 0.05$). Interestingly, the BP decrease induced by combination therapy may be prolonged up to 24 h, and may improve BP variability, what has been shown by evaluating the trough-to-peak ratio and smoothness index of different combinations, particularly combinations of a RAAS blocker with a diuretic or a CCB [18,19]. Even for short acting drugs as losartan, which not covers the entire 24-hour period when given once daily in monotherapy, its combination with a thiazide diuretic improves the trough-to-peak ratio of losartan alone and maintain the 88 % of the maximal effect 24 h after been administered [20].

The use of combination therapy with a single pill combination (SPC) has the advantage of simplifying the treatment algorithm and reducing the total pill burden for patients (Table 2). The Simplified Treatment Intervention to Control Hypertension Study was conducted using a cluster randomized trial design in 45 family practices in southwestern Ontario to examine a simplified intervention focused on initial treatment with SPC consisting of either a low-dose ACE inhibitor with

Table 2
Advantages and disadvantages of single pill combination therapy versus monotherapy for management of hypertension.

Single pill combination	Monotherapy
Advantages	
Targets multiple blood pressure pathways	Greater flexibility in medication dosing regimens
Simplifies treatment regimen and lowers pill burden	Easier to identify side effects
Reduces clinical inertia and achieves target blood pressure more often	May be better suited for some High-normal/Grade 1 hypertensive patients
Fewer side effects with low dosing of medications	May be safer for frail, older patients
Combines first-line medication classes	Can be lower in cost than some single pill combinations
Disadvantages	
Some combination pills may be more expensive	Targets a single pathway in blood pressure
Less flexibility in medication dosing	Less effective than combination therapy
Inability to isolate cause of medication side effects	Greater risk of clinical inertia

diuretic or ARB with diuretic [21]. The control group was treated according to the Canadian Hypertension Education Program Guideline which recommended initial monotherapy with a thiazide diuretic and the addition of calcium channel blocker (CCB), ACE inhibitor, ARB, or beta-blocker if standard dose monotherapy did not achieve target BP control (<140/90 mm Hg) [22]. At 6 months, multivariate modeling demonstrated that patients treated with SPC therapy were 20 % more likely to achieve target BP control compared to those in the usual care group (65 % versus 53 %, $p = 0.028$).

SPC therapies combining low doses of three first line BP lowering agents are also available. The TRIUMPH study group investigated the efficacy of a low dose, triple SPC containing telmisartan 20 mg, amlodipine 2.5 mg, and chlorthalidone 12.5 mg among 675 participants in Sri Lanka [23]. The primary BP goal was <140/90 mm Hg and <130/80 mm Hg for participants with diabetes or chronic kidney disease (CKD). Among participants in the triple SPC group, 70 % achieved target BP control at six months compared to 55 % in the usual care group ($p < 0.001$). Additionally, the triple SPC group had a 9.8 mm Hg greater SBP reduction (95 % CI −7.9 to −11.6 mm Hg, $p < 0.001$) compared to the usual care group.

The QUARTET trial investigated the efficacy of a low dose, quadruple SPC (irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.65 mg, and bisoprolol 2.5 mg) compared to irbesartan 150 mg monotherapy [24]. At one year follow-up, individuals in the quad pill group were 32 % more likely to have controlled BP <140/90 mm Hg (HR 1.32, 95 % CI, 1.16–1.50, $p < 0.0001$). SBP was 7.7 mm Hg (95 % CI 5.2–10.3 mm Hg) lower in the SPC group compared to individuals in the monotherapy group. At the 12-week follow-up visit, 40 % of participants in the monotherapy group had a clinical indication for additional BP medication compared to 15 % in the quad pill group.

The superior efficacy of combination therapy is also supported by real world data from observational studies. In a retrospective analysis of >100,000 patients seen at 180 practice sites, Egan et al. used electronic health records to examine the initial BP treatment approaches of monotherapy, free pill combination, and SPC [25]. Approximately three quarters of patients were initiated on monotherapy, 17 % on multipill combinations (MPC), and 9 % on SPC. Among patients started on SPC, 68 % achieved BP target (<140/90 mm Hg or <130/80 mm Hg for participants with diabetes or CKD) after one-year follow-up compared to 59 % who were initiated on MPC or monotherapy. The median time to achieve BP control) in half of the patients was shortest for those on SPC at 195 days compared to 269 days for those on MPC and 280 days for those on monotherapy ($p < 0.001$). After adjusting for differences in risk factors, patients started on SPC were 53 % more likely to achieve BP control (HR 1.53, 95 % CI 1.47–1.58) and those on MPC were 34 % more likely to achieve BP control (HR 1.34, 95 % CI 1.31–1.37) compared to patients started on monotherapy.

While there are no randomized controlled trials comparing monotherapy to combination therapy and cardiovascular disease (CVD) outcomes, observational data suggests lower CVD event rates associated with combination treatment. A propensity matched analysis of more than 17,000 patients in Taiwan using the National Health Insurance Research Database examined CVD outcomes for patients prescribed a fixed dose SPC or MPC with a renin angiotensin system inhibitor and thiazide diuretic [26]. Individuals were matched in a 3:1 ratio based on CVD risk factors, medication use, and comorbidities. They found that subjects on fixed dose combination had a 15 % lower risk for major adverse cardiovascular events (all-cause mortality, myocardial infarction, stroke, and coronary revascularization) ($p = 0.017$) compared to those prescribed individual combination therapy.

Another potential advantage of initial combination treatment is that it can reduce clinical inertia, a major cause of patients not achieving BP control [27]. Using data from the Italian National Health Service, Rea et al. examined 125,000 patients with a new prescription for antihypertensive medication of whom 80 % were initially prescribed monotherapy and the remainder combination treatment with either a two drug SPC or MPC [28]. At three years follow-up, 78 % of patients started on combination therapy remained on combination therapy, while only 36 % of patients started on monotherapy had an additional agent prescribed (HR 2.23, 95 % CI 2.19–2.27). In a propensity matched analysis, those on either a two drug SPC or MPC had a 16 % lower risk of CVD events (HR 0.85, 95 % CI 0.79–1.09) and 20 % lower risk for death (95 % CI 0.72–0.89) compared to persons started on monotherapy.

An alternative approach to overcome clinical inertia is the strategy of using milepost visits employed in the Systolic Blood Pressure Intervention Trial (SPRINT) [29]. Participants began the study on two or three antihypertensive medications, with possible exceptions for patients who were >75 years old and SBP <140 mm Hg. Milepost visits occurred every six months, at which time if a participant in the intervention group had a systolic blood pressure >120 mm Hg, titration of current blood pressure medications was not allowed and the initiation of an additional BP medication class was mandated. This strategy led to achievement of a median SBP of 118 mm Hg at 36 months compared to a median SBP of 136 mmHg for the usual care group with on average only one additional medication prescribed (2.8 versus 1.8) to achieve <120 mm Hg BP goal [30].

3. Combination treatment reduces individual side effects of the individual components

A major advantage of combination therapy is that, in general, lower medication doses are less likely to cause adverse effects compared to higher doses. In a meta-analysis of 354 clinical trials, Law et al. examined the relationship between antihypertensive medication dose and adverse effects [31]. They found that as the dose increased from half standard to standard to twice standard dose, the percentage of individuals with side effects increased for those prescribed thiazide diuretics or CCB, but not ACE inhibitors or ARBs. At half standard dosing, all four of these antihypertensive classes had up to 3.9 % higher rates of adverse effects compared to the placebo group. At standard dosing, 8 % of patients taking CCB, 10 % taking thiazides, 4 % taking ACE inhibitors, and 0 % taking ARBs reported side effects that increased to approximately 15 %, and 18 %, respectively, at twice standard dosing, while there was no to minimal increase for participants taking ARBs (3.9 % versus 3.9 %) or ACE inhibitors (0 % versus 2 %).

These findings extend to participants on three or four classes of SPC medications at low doses. In the TRIUMPH study, individuals randomized to triple SPC did not experience higher rates of adverse events ($p = 0.82$) or withdrawal from BP lowering therapy compared to individuals receiving usual care ($p = 0.92$) [23]. In the QUARTET trial, individuals on a SPC with a quarter dose of four different medications also experienced no difference in adverse events leading to treatment withdrawal ($p = 0.27$) [32]. Even with the aggressive <120 mm Hg SBP goal in the SPRINT trial, there was no significant difference in the total number of serious adverse events between the intensive and standard treatment groups ($p = 0.25$). However, the smaller number of serious adverse events thought to be possibly or definitely related to the intervention in SPRINT was significantly higher in the intensive treatment group (4.7 % versus 2.5 % $p < 0.001$).

The use of combination therapy can also help to counteract major side effects when chosen based on synergistic mechanisms of action. One of the most common side effects of first-line antihypertensive medications is the derangement in serum potassium levels. Diuretics can cause hypokalemia, while ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists can cause hyperkalemia. Therefore, many combination pills combine a diuretic with either an ACE inhibitor or ARB. Pool et al. examined the efficacy and tolerability of valsartan 160 mg/320 mg or hydrochlorothiazide (HCTZ) 12.5 mg/25 mg monotherapy versus high dose combinations of valsartan and HCTZ in patients with primary hypertension [33]. Combination therapy was associated with greater reductions in BP compared to monotherapy and lower frequency of hypokalemia compared to HCTZ alone. Hypokalemia (serum potassium

<3.2 mEq/L) occurred in 7.1 % and 13.3 % of patients randomized to 12.5 mg and 25 mg of HCTZ, respectively, versus 1.8 % and 6.1 % in the combination arm, valsartan 160 mg/HCTZ 12.5 mg and valsartan 320 mg/HCTZ 25 mg, respectively.

In a study of 252 individuals who developed hypokalemia while taking hydrochlorothiazide, Schnaper et al. compared the addition of potassium 20 mmol/day, potassium 40 mmol/day, or the potassium sparing diuretic triamterene at a dose of 75 mg per day [34]. They found that within one week there was an increase in the mean serum potassium, which remained at a constant level four weeks after initiation. Patients prescribed the combination of hydrochlorothiazide 50 mg plus triamterene 75 mg had a similar increase in serum potassium compared to those prescribed 40 mmol of potassium.

CCBs can cause peripheral oedema via arteriolar dilation and capillary leakage, often leading to medication discontinuation [35]. However, the combination of renin-angiotensin system blockers with CCB can significantly reduce the risk of peripheral oedema by reducing post-capillary resistance [36]. In a meta-analysis of 25 randomized controlled trials with >17,000 patients, Makani et al. found that individuals prescribed a renin angiotensin system blocker with a CCB were 38 % less likely to experience peripheral oedema compared to CCB monotherapy (3.2 % versus 6.0 %, $p < 0.0001$) and a 62 % lower likelihood of CCB therapy discontinuation (RR 0.38, 95 % CI 0.22–0.66, $p < 0.0001$) [37]. ACE inhibitors appeared to be more effective in reducing the incidence of peripheral oedema (RR 0.46, 95 % CI 0.37–0.58, $p < 0.0001$) compared to ARBs (RR 0.79, 95 % CI 0.64–0.97, $p = 0.02$), although they were not directly compared for statistical significance.

While side effects of antihypertensive therapies can be mitigated by use of appropriate combination classes, inappropriate addition of medications to treat side effects has been observed. Vouri et al. examined more than 1 million patients with a new prescription for a CCB and subsequent prescribing patterns [38]. They found that the secular trend adjusted sequence ratios (aSR) for prescription of a new loop diuretic were higher for individuals prescribed a high dose of a CCB (aSR 2.20, 95 % CI 2.13–2.27), suggesting that loop diuretics were prescribed to treat the side effect of peripheral oedema from CCB rather than discontinuing the CCB and switching to a different BP medication. Another important consideration for SPC and MPC is that if side effects do occur, it may be more difficult to determine which is the causative medication. Starting with higher doses of SPC and MPC is also more likely to cause symptomatic hypotension, which is an important consideration for frail older persons who are more susceptible to serious adverse events from rapid lowering of BP [39].

4. Combination treatment in a single pill improves therapeutic adherence and persistence

As mentioned before, all current data show that BP control is poor in high-income and low-income countries [9,10]. Many factors can explain poor BP control, some of them related to patient (lack of symptoms, lack of understanding of disease and of treatment need, possible or experienced adverse effects, perceived lack of treatment benefit, or treatment interference with patient's daily schedule, among others), some others related to physicians (physician inertia, regimen complexity, prescription errors, lack of guidelines knowledge or training, time constraints, communications skills), and unsupportive healthcare systems (access to care, medication cost and affordability) [40], low adherence to antihypertensive medication is recognized in all guidelines as a major contributor to poor BP control rates [11–15]. Many studies confirm that poor adherence to medications exists even in the highest-risk secondary prevention patients [41–44].

In a meta-analysis including nearly two million participants, good adherence to CVD medications was associated with a 20 % (95 % CI: 16–23) lower risk of CV events and 38 % (95 % CI: 23–43) lower risk of all-cause mortality. Moreover, high adherence (≥ 80 % of prescribed drugs) to antihypertensive drugs has been shown to reduce MACE by 19 % (95 % CI: 14–24) and all-cause mortality by 29 % (95 % CI: 22–36) in highly adherent versus poorly adherent (< 80 % of prescribed drugs) hypertensive patients [45]. Observational data from the Lombardy region in Italy [46] demonstrate that adherence to antihypertensive drug therapy reduces the risk of CV outcomes by 37 % (95 % CI: 34–40), and good adherence with antihypertensive medication was associated with a 40 % (95 % CI: 38–42) lower risk of CV mortality even in old frail patients with very poor clinical conditions [47].

When looking at adherence from the clinician's perspective, the patient-clinician relationship is a key element for both assessing adherence and selecting interventions tailored to the patient's profile [48–50]. There is robust evidence supporting that the number of prescribed pills is inversely related to adherence to treatment [51–55]. The number of prescribed drugs was directly associated with an increased risk of non-adherence from 74 % (95 % CI: 32–129) to 85 % (95 % CI: 58–116) in different studies [51,52], and a simple and easy measure such a simplification of treatment regimens by reducing the number of pills from two (in free equivalent combination) to one (single pill combination) may have an important positive impact improving 78 % adherence and 87 % persistence on medication [54], with the consequent reductions of CVD outcomes (about 11 % to 17 %) and healthcare costs [55–58]. Fig. 1 summarizes the advantages and disadvantages of selecting SPC therapy over a free pill equivalent combination (FEC).

A systematic review and meta-analysis of 44 studies assessed whether SPC therapy led to improved adherence, persistence, and better BP control compared with FEC therapy in adults aged ≥18 years with hypertension receiving SPC or FEC antihypertensive therapy [54]. Adherence, persistence, and reductions in systolic BP and/or diastolic BP were measured and compared. Most of the studies (18 of 23) showed that adherence was significantly improved in patients receiving SPC in comparison with those receiving FEC. Sixteen studies measured persistence, of which 14 (87 %) showed that patients receiving SPC had significantly improved persistence, or were significantly less likely to discontinue therapy than patients receiving FEC. SBP (mean difference, −3.99 mmHg; 95 % CI, −7.92 to −0.07; $P = 0.05$) and DBP (−1.54 mmHg; 95 % CI, −2.67 to −0.41; $P = 0.0076$) were both significantly reduced with SPC therapy compared with FEC therapy at week 12. Fig. 2 summarizes the results of 44 studies comparing adherence in patients treated with SPC vs FEC antihypertensive strategy. A significantly higher percentage of patients on SPC therapy had improved adherence and persistence, compared with those treated with FEC. About one third of these patients have greater absolute reductions of SBP and DBP, and improved BP control [54].

SPC therapy offers a number of potential advantages over FEC therapy, including improved tolerability, reduced pill burden, lower medical costs and resource utilization, reduced clinical inertia, and improved patient medication adherence, leading to improved BP control rates in hypertensive patients ([11-15,58]). A recent statement by the American Heart Association concluded that simplifying treatment regimens by using fixed-dose combinations of antihypertensive drugs in a SPC and polypills containing a statin plus BP-lowering drugs should be recommended [49]. Most international guidelines recommend simplifying drug regimens and favour the use of SPC therapy for the majority of patients to improve adherence, persistence, BP control, and cardiovascular morbidity and mortality [11–15].

Increased efforts by local, regional, and national health authorities to place SPC in drug formularies for the treatment of hypertension would be desired. As CVD rates are rising in low-income countries and maintaining in high-income countries, implementation of more innovative strategies aimed at the prevention, diagnosis, and treatment of hypertension is paramount. The use of SPC therapy for the initial treatment of hypertension, as recommended in most international BP guidelines, is a key strategy to address this complex public health problem.

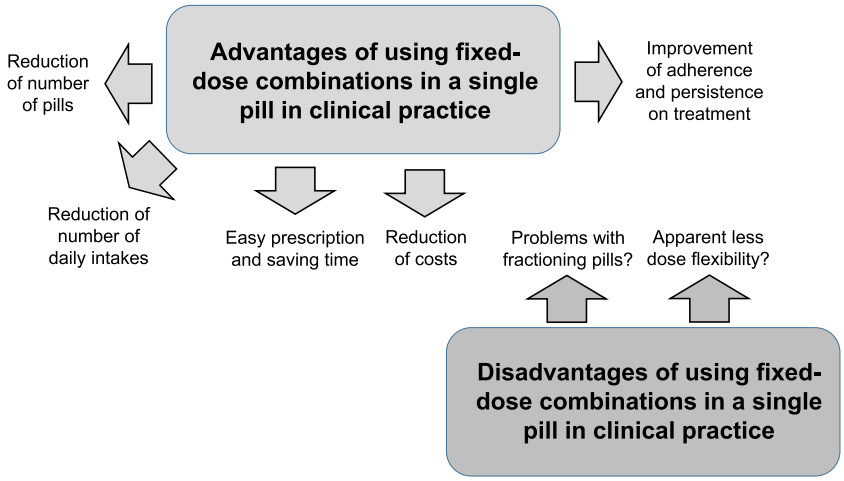

Fig. 1. Key points in the selection of the best therapeutic strategy in hypertension: Advantages and possible disadvantages of selecting single pill combinations versus free combinations in the antihypertensive treatment strategy.

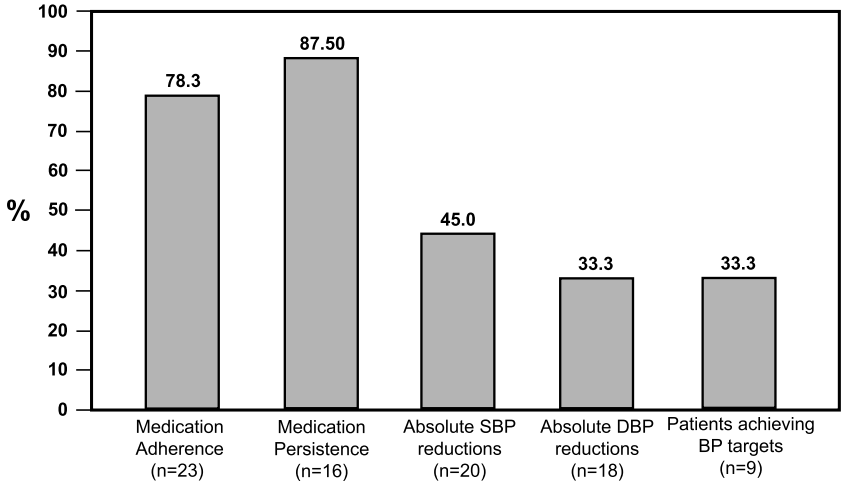

Fig. 2. Patients (%) improving adherence, persistence, absolute reductions of systolic (SBP) and diastolic (DBP) blood pressure, and BP control when treated with single pill combination, compared to free combination strategies in 44 studies. Parenthesis indicate the number of studies in which each parameter was analysed. Data obtained from reference 50.

5. Combination treatment achieves earlier blood pressure control

Although clinical practice guidelines recommend a BP threshold to initiate treatment and BP targets to be achieved in hypertensive patients based on CVD risk profiles, the optimal timeframe for achieving BP control is not well defined. A series of landmark BP intervention trials in patients with hypertension and additional cardiovascular risk factors demonstrate that prompt BP control within 1 to 3 months can improve cardiovascular outcomes, particularly in high risk patients [59].

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial compared the antihypertensive efficacy of the CCB amlodipine versus the ARB valsartan. It was one of the first trials supporting the beneficial effects of early BP control on MACE in high-risk hypertensive patients. The study found that achieving SBP below 140 mm Hg within six months, or "immediate response," was associated with a significant decrease in CVD outcomes ($p > 0.05$), regardless of the medication chosen. Immediate responders were either patients who were previously untreated and had a SBP reduction of 10 mm Hg within the first month, or those whose BP did not increase after switching to the trial's prescribed medications. They had significantly lower rates of combined cardiac events ($p < 0.05$), stroke ($p < 0.05$), and all-cause mortality ($p < 0.05$) [60].

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) found a significant correlation between BP control within a six-month period (SBP 148.94±15.43 vs. 146.15±15.63 mmHg; $p < 0.001$) and risk of stroke. Non-immediate responders were more likely to have heart failure (HF), coronary artery disease (CAD), and combined cardiovascular disease [61]. The Anglo-Scandinavian Cardiac Outcomes Trial-BP Lowering Arm (ASCOT-BPLA) attributed the early BP lowering effect of amlodipine to its superiority in reducing the primary endpoint of non-fatal MI plus fatal CHD (HR 0.64; 95 %CI: 0.50–0.83; $p = 0{\cdot}0005$), and the secondary endpoints of total CV events and procedures (HR 0·79; 95 %CI: 0·69–0·90; $p = 0{\cdot}0005$), fatal and non-fatal MI (HR 0.62; 95 %CI: 0.47–0.81; $p = 0{\cdot}0005$) and total coronary events (HR 0.71; 95 %CI: 0.59–0.88; $p = 0{\cdot}0005$) [62].

The Study on Cognition and Prognosis in the Elderly (SCOPE) also found that early BP pressure control during the first three months of treatment (difference in SBP/DBP −3.7/−1.8 mmHg) was associated with lower risk of stroke [63]. A recent meta-analysis demonstrated that achieving a SBP/DBP reduction > 10/5 mmHg within a year decreased the incidence of CAD events by 22 % (95 % CI: 15–28), stroke by 37 % (95 % CI: 29–44), and HF by 46 % (95 % CI: 36–55) with this impact sustained over 4 years of follow-up [64]. These results show that earlier

BP control is associated with better and persistent cardiovascular protection. What remains unclear is the optimal window of time to achieve BP targets to reduce cardiovascular events [65,66].

The ACCOMPLISH TRIAL evaluated the effectiveness of SPC therapy as an initial treatment for 10,704 high-risk hypertensive patients. After 6 months of treatment, BP control rates were 73 % in the overall trial (BP < 140/90 mmHg), 43 % in diabetics (BP < 130/80 mmHg), and 40 % in patients with CKD (BP < 130/80 mmHg). Of note, 61 % of uncontrolled patients were not taking their recommended treatment dosage. Only 1.8 % of subject reported symptoms of hypotension. This trial report showed that the initial combination therapy algorithm, benazepril plus amlodipine or benazepril plus hydrochlorothiazide, is safe and quick to induce BP control during the first six months of treatment in most hypertensive patients, including those at high risk [67].

Another trial aimed at examining the safety and effectiveness of dual vs. triple antihypertensive combination therapies in patients with mild to severe hypertension involved 245 participants randomly assigned to either the dual combination (amlodipine plus losartan, losartan plus chlorthalidone, and amlodipine plus chlorthalidone,) or triple combination of all three agents. The triple combination group significantly dropped SBP at weeks 4 and 8 (BP reduction −18.3 ± 13.2 mmHg at week 8) compared to any of the dual combination groups (BP reduction −13.0 ± 13.3 mmHg; −16.3 ± 12.4; and-13.8 ± 13.2 mmHg respectively). The triple combination group had also a larger proportion of SBP control at 4 weeks (46.2 % compared to 22.0 % ($P = 0.013$); 23.3 % ($P = 0.021$); and 27.1 % ($P = 0.045$) dual combination groups respectively. Triple antihypertensive combination therapy showed early and effective BP management without increasing adverse events in patients with mild-to-moderate hypertension [68].

A multicentre double-blind study was conducted to determine if combining telmisartan and nifedipine GITS at a low dose reduced 24-hour ambulatory BP (ABPM) and clinic BP more than either of the two agents used as monotherapy. The study involved 405 patients with clinic SBP above or equal to 135 mmHg and a history of diabetes, metabolic syndrome, or hypertension mediated organ damage. After 16 weeks of follow-up, patients receiving monotherapy were transitioned to combination treatment. Either clinic and 24h-ABPM SBP values were significantly reduced by all strategies ($P < 0.0001$), and 24h-ABPM reduction was significantly higher in the combination arm compared to any monotherapy arm at 8 weeks (10.8 ± 0.8 vs. 6.6 ± 1.1 mmHg in the telmisartan ($P = 0.001$) and 8.0 ± 1.2 mmHg in the nifedipine GITS ($P = 0.037$) groups respectively). After 16 and 24 weeks of treatment, switching from monotherapy to combination therapy enhanced the antihypertensive effect resulting in similar ambulatory and clinic SBP and DBP reductions for all three groups. Combination treatment with low dose nifedipine GITS and telmisartan reduced clinic and 24h-ABPM more effectively and much sooner than each as a monotherapy. However, initiating treatment with the combination did not lead to better long-term BP control compared to starting treatment with monotherapy and switching to the combination later [69].

The ADVISE study compared high-dose valsartan monotherapy (160 mg/d) with combination therapy of nifedipine GITS 30 mg/d and valsartan 80 mg/d in Asian patients with hypertension. The study compared mean changes in clinic SBP and DBP, adverse events, response rate, and BP control rate at 12 weeks. The combination of half dose nifedipine GITS plus valsartan significantly showed higher BP control rates at week 4 (51.2 %) than high dose valsartan monotherapy (38.4 %; $P = 0.0138$), and increased after 12 weeks (71.2% vs. 55.5 %; $P = 0.0024$). The mild-to-moderate adverse event rates (4.5% vs 4.4 %) were comparable between the two arms [70].

The Triple Pill vs. Usual Care Management for Patients with Mild-to-Moderate Hypertension (TRIUMPH) trial was conducted in urban hospital clinics in Sri Lanka between February 2016 and May 2017. The trial compared usual care with once-daily single pill fixed-dose triple combination of telmisartan 20 mg, amlodipine 2.5 mg, and chlorthalidone 12.5 mg in patients with mild to moderate hypertension. Over 700 patients were randomly assigned, and the triple SPC group experienced longer time at target BP over 24 weeks of follow-up (64% vs 43 %; risk difference, 21 %; 95 % CI, 16–26; $P < 0.001$). More than twice as many patients receiving triple SPC therapy achieved more than 50 % time at target (64% vs 37 %; $P < 0.001$). Triple SPC was associated with an increased time at target, with the majority reaching more than 50 % of their target. At every follow-up period, triple SPC recipients outperformed usual care recipients in terms of time at target BP (6 weeks, 36.3 ± 30.9% vs 21.7 ± 28.9 %, $P < 0.001$; 12 weeks, 52.2 %±31.9% vs 33.7 ± 33.0 %, $P < 0.001$; 24 weeks, 66.0 ± 31.1% vs 43.5 ± 34.3 %, $P < 0.001$). This study offers the first approximation of time at target for evaluating longitudinal BP management in a randomized clinical trial [71].

Based on this evidence, the 2023 ESH hypertension guidelines [15] recommend achieving BP target within the first three months after initiation of treatment for all patients with hypertension, regardless of global CV risk or grade of hypertension, and starting with dual SPC therapy and escalating to triple SPC therapy when needed.

6. Optimization of cardiovascular prevention with single pill combination of blood pressure lowering drugs, lipid-lowering drugs and aspirin: the polypill

In 2001, the cardiovascular polypill concept was proposed by the World Health Organization and Wellcome Trust expert group [72] as a combination of medications with proven CVD benefits (beta-blocker, ACEI, statin, and aspirin) in a single pill. It was suggested that its use might reduce CVD events in people at high risk of CVD. Two years later, Wald and Law showed that a polypill combining five medications and a vitamin (three antihypertensive agents, statin, aspirin, and folic acid) could reduce the risk of acute myocardial infarction by 88 % (95 % CI: 84–91 %) and stroke by 80 % (95 % CI: 71–87 %) [73]. Currently, the most accepted definition is one proposed by the World Heart Federation that is defined as a SPC therapy that includes one or two antihypertensive agents and a statin, with or without aspirin [74].

6.1. *Rationale for the use of a polypill*

The use of evidence-based pharmacotherapy is a mainstay in CV risk management. In secondary prevention, combining an antiplatelet agent, ACEI or ARB, beta-blocker, and statin decreases the risk of all-cause mortality by 40 % (95 % CI: 34–45 %), myocardial infarction by 27 % (95 % CI: 17–36 %) and stroke by 21 % (95 % CI: 9–32 %) compared to monotherapy or no therapy [75]. However, the Prospective Urban Rural Epidemiology (PURE) study revealed a low use of these therapies worldwide [76]. For example, in South American countries, the overall use of the four drugs was only 4.1 % [77]. The world, multiregional survey INTERASPIRE reported that less than half of the participants were taking the four therapies drugs for secondary prevention [78]. These low treatment rates have been attributed to barriers including low availability, accessibility, and affordability of the medications [79]. At the individual level, patients at high risk for CVD require a complex and broad medication regimen, which translates to increased pill burden and multiple daily dosing, both predisposing factors to lower adherence and persistence in treatment [80]. It has been proposed that some of these barriers could be addressed with the polypill strategy.

6.2. *Polypill in primary prevention*

After the landmark meta-analysis by Wald and Law [73], studies have been conducted in primary prevention, including the International Polycap Study (TIPS). The phase 2 TIPS study evaluated the efficacy of the Polycap (hydrochlorothiazide 12.5 mg, ramipril 5 mg, atenolol 50 mg, simvastatin 10 mg, and aspirin 100 mg) to reduce BP and LDL-C levels. In 2053 adults with at least one CV risk factor, the Polycap lowered SBP by 7.4 mmHg (95 % CI, 6.1–8.1 mmHg) and DBP by 5.6

mmHg (95 % CI, 4.7–6.4), which was similar when three BP-lowering drugs were used, with or without aspirin. Reductions in BP increased with the number of drugs used (2.2/1.3 mmHg with one drug, 4.7/3.6 mmHg with two drugs, and 6.3/4.5 mmHg with three drugs). LDL-C was reduced by 0.70 mmol/L (95 % CI: 0.62–0.78) equivalent to 27.0 mg/dL, similar to standard treatment after eight weeks of follow-up [81]. Subsequently, the TIPS-2 study increased the doses of Polycap, showing a further reduction of LDL-C by 6.6 mg/dL and, consequently, a theoretical greater reduction in CVD risk [82]. The TIPS-3 study [83] evaluated 5713 adults with intermediate or high CVD risk and showed that after a 4.6-year follow-up, the Polycap plus aspirin reduced the composite primary outcome (CV death, myocardial infarction, stroke, heart failure, cardiac arrest) by 31 % compared to the control group (HR: 0.69; CI 95 %: 0.50 −0.97).

Likewise, the PolyIran study, a pragmatic, cluster-randomized trial, randomized 6838 participants with and without a history of CV disease to a polypill strategy or usual care. The polypill was composed of hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg, and enalapril 5 mg (in case of cough enalapril was replaced by valsartan 40 mg). After a median follow-up of 60 months the intervention arm reduced MACE by 34 % (HR: 0.66; 95 % CI: 0.55–0.80) [84]. Furthermore, a meta-analysis of 3 randomized controlled trials (TIPS-3, HOPE-3, and PolyIran) with 18,162 adults at intermediate CVD risk showed that polypill decreased a composite outcome of CV death, myocardial infarction, stroke, or revascularization by 38 % (95 % CI: 27–47 %, $P < 0{\cdot}0001$) compared to standard treatment, after a median follow-up of 5 years. The addition of aspirin showed an increased 47 % reduction in the main outcome (95 %CI: 33–59 %) [85]. Therefore, SPC therapy of antihypertensive drugs with statin, with or without aspirin, substantially reduced MACE in primary prevention, with greater reductions in those receiving aspirin.

6.3. Polypill in secondary prevention

Considering the key role of pharmacological treatment in secondary prevention of CV disease, several polypill studies have been conducted. The Neptuno study was a retrospective cohort study with data from electronic health records [86]. After propensity score matching, it was demonstrated that the polypill developed by the Centro Nacional de Investigaciones Cardiovasculares (CNIC) in Spain, the CNIC-Polypill, containing aspirin 100 mg, atorvastatin 20/40 mg, and ramipril 2.5/5/10 mg, administered once daily improved BP (12.5% vs 6.3 %; $p < 0.05$) and LDL-C (10.3% vs 4.9 %; $p < 0.001$) control rates compared to standard treatment. The incidence of recurrent MACE was lower in the polypill cohort (19.8 %) compared to the cohort using medications separately (23.3 %) ($p < 0.001$). The Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) study, randomized 2499 participants with history of myocardial infarction in the previous six months to a polypill-based strategy with the CNIC-Polypill or usual care. At three years of follow-up, the risk of MACE was reduced by 24 % (HR: 0.76; 95 %CI: 0.60–0.90), and CV death by 33 % (HR: 0.67; 95 % CI: 0.47–0.97) in the polypill arm [87]. Similarly, the PolyIran trial reported a 20 % reduction in MACE in the secondary prevention group (HR: 0.80; 95 % CI: 0.57–1.12) during 5 years of follow-up. Not surprisingly, participants who achieved greater adherence using the polypill had a lower rate of MACE (Number Needed to Treat (NNT) of 20.7 to prevent one MACE) [84].

Despite these results, a meta-analysis of 8 studies with 25,584 patients [88] found no differences in MACE (RR: 0.85; 95 % CI: 0.70–1.02) in secondary prevention patients with polypill intervention, but significant reductions in the risk of all-cause mortality (RR: 0.90; 95 % CI: 0.81–1.00). However, this meta-analysis had a significant degree of heterogeneity, especially when evaluating adherence and treatment discontinuation, making it difficult to extrapolate their findings. Overall, it appears that polypill strategy may reduce the risk of recurrent CV events, and use of a once-daily fixed-dose cardiovascular polypill should be integrated into clinical practice [89,90].

6.4. Safety of the polypill

A major reason to promote SPC strategy is that combining different classes of medications will improve efficacy while reducing side effects due to lower medication dosing. Participants using a polypill did not experienced fewer side effects compared to those assigned to usual care. Therefore, reducing side effects of individual medications does not represent an important reason for its clinical use [91]. Given the high prevalence of comorbidities in subjects with established CVD, careful review of each polypill component is essential. For example, a polypill containing aspirin should be avoided in patients who require long-term or permanent chronic anticoagulation. Additionally, polypills should not be prescribed for patients with heart failure when an ARB/neprilysin inhibitor is indicated [89,90].

6.5. Possible explanations of its benefits

In addition to its efficacy in reducing MACE, polypills increase medication adherence [91]. A higher adherence could be driven by a reduction in pill burden, enhanced patient preferences, less therapeutic inertia, and a synergistic effect of the individual components of the pill [80]. The polypill has been shown to improve quality of life. In the AURORA study, it was reported that 98 % of participants would choose a medication regimen that included the polypill, with 92 % highlighting the ease of use, and 97 % considering the polypill practical and feasible [92]. Similarly, the participants in the polypill arm of the IMPACT study more frequently reported "very easy" use of this strategy compared with usual care (53% vs. 46 %) [93]. Therefore, regimen simplification is effective in addressing low medication adherence [55,55]. A meta-analysis of 8 randomized clinical trials with 25,584 adults showed improvement in adherence with polypill (HR: 1.31; 95 %CI: 1.11–1.55) [88]. In a recent review including real-world data, the polypill improved overall medication adherence by 13 % (95 % CI, 7.6 % to 34.9 %) compared with standard medication [91]. For clinicians, prescribing a polypill may reduce therapeutic inertia and improve patient adherence.

6.6. Guidelines recommendations on the clinical use of polypills

Based on the results of clinical trials demonstrating the potential benefits of CV polypills to increase adherence and reduce MACE, the 2023 ESC Guidelines for the Management of Acute Coronary Syndromes recommend polypills as an option to improve adherence and outcomes in secondary prevention (CoR IIa – LoE B) [94]. Furthermore, the 2023 ESH Guidelines for the management of arterial hypertension recommends polypills in both primary and secondary prevention, clarifying that those with aspirin should be preferred in secondary prevention and polypills without aspirin in primary prevention (CoR II LoE A) [15]. However, some barriers to the routine use of a polypill in clinical practice must be addressed and overcome. First, the adoption of multiple combination dosing regimens of antihypertensive medications and statin to achieve BP and cholesterol targets is difficult. Second, the inclusion of dual antihypertensive therapy in some polypills to follow the recommendations of current guidelines. Third, finding the correct combination of antihypertensive drugs in the polypill may be problematic since the antihypertensive agents recommended for primary prevention (ACEi or ARB plus CCB or thiazide diuretic) differ from antihypertensive therapies required for secondary prevention (e.g. beta-blocker instead of diuretic). Finally, standardized clinical algorithms with polypills for primary and secondary prevention will require more validation before their widespread use [80,89,90].

Declaration of competing interest

The authors declare they have no conflict of interest.

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